Research Journal of Pharmacology and Toxicology 01[02] 2015
www.asdpub.com/index.php/rjpt

Review Article

Review on antimicrobial potentials of quinolone derivatives

Mohammad Asif*

Department of Pharmacy, GRD (PG) Institute of Management & Technology, 248009, Dehradun, (Uttarakhand), India

***Corresponding Author**
Mohammad Asif
Department of Pharmacy,
GRD (PG) Institute of Management & Technology,
248009, Dehradun, (Uttarakhand), India
E-mail: aasif321@gmail.com

Keywords:
Quinolones;
Antimicrobial;
Bacterial infections;
Resistance

Abstract

The quinolones are a class of bicyclic molecules, organic chemical structures that are related to the heteroaromatic coal tar isolate quinoline. Quinolone antibacterials are widely used. Specific quinoline molecules substituted with an hydroxyl functional group at carbons 2 and 4 are most often observed in isomeric forms termed 2- and 4-quinolones, respectively. The relative importance of 4-quinolones has increased with the discovery that such structures that also bear a carboxylic acid (-COOH) and other functional groups at particular sites on the ring have very potent bacteriocidal activities, inhibiting of a broad spectrum of Gram negative and Gram positive DNA gyrase and topoisomerase enzymes. Hence, they are very useful in antibacterial therapy.

1. Introduction

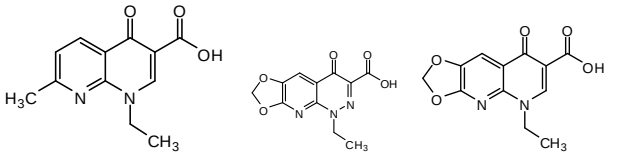
The quinolones are a family of synthetic broad-spectrum antibacterial drugs [1-3]. The first generation of quinolones began with the introduction of nalidixic acid for treatment of urinary tract infections in humans [4]. Nalidixic acid was discovered in a distillate during an attempt at chloroquine synthesis [5]. Quinolones exert their antibacterial effect by preventing bacterial DNA from unwinding and duplicating [6]. The majority of quinolones in clinical use belong to the subset fluoroquinolones (FQLs), which have a fluorine atom attached to the central ring system, typically at the 6-position or C-7 position.

1.1 History

Nalidixic acid is considered to be the predecessor of all quinolone family, including the second, third and fourth generations commonly known as fluoroquinolones (FQLs). Though it is generally accepted nalidixic acid is to be considered the first quinolone drug, this has been disputed over the years by a few researchers who believe chloroquine, from which nalidixic acid is derived, is to be considered the first quinolone drug, rather than nalidixic acid. The 1,8-naphthyridine-type agent nalidixic acid, is the predecessor of quinolone antibacterials, the matter has been contested by a few researchers who promote chloroquine, from which nalidixic acid was derived. The various quinolones are nalidixic acid, extensive quinolone family, which includes second, third, and fourth generation quinolones, and further agents under development. This first, nalidixic acid generation included other such "quinolone" drugs as oxolinic acid (a true 4-quinolone), pipemidic acid (a pyridopyrimidine), and cinoxacin (a cinnoline), all introduced in the 1970s. Each proved to be only marginal improvements over nalidixic acid [7]. Since the introduction of nalidixic acid in 1962, more than 10,000 quinolone analogs have been synthesized; and as is standard in modern medicinal chemistry, a handful have found their way into wide clinical practice [8,9].

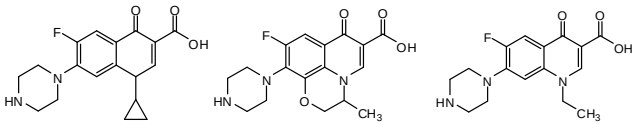
2. Quinolones as antibacterials

Quinolones are a family of synthetic broad-spectrum agents used as anti-bacterial agents [3]. The first generation of the quinolones began following introduction of the related, but structurally distinct naphthyridine-family nalidixic acid in 1962 for treatment of urinary tract infections in humans [4]. Nalidixic acid was discovered by George Lesher and coworkers in a chemical distillate during an attempt at synthesis of the chloroquinoline antimalarial agent, chloroquine [5]. Naphthyridone and quinolone classes of antibiotics prevent bacterial DNA replication by inhibition of DNA unwinding events, and can be both bacteriostatic and bacteriocidal [6]. The majority of quinolones in clinical use belong to the second generation class of "fluoroquinolones", which have a true quinoline framework, maintain the C-3 carboxylic acid group, and add a fluorine atom to the all-carbon containing ring, typically at the C-6 or C-7 positions.

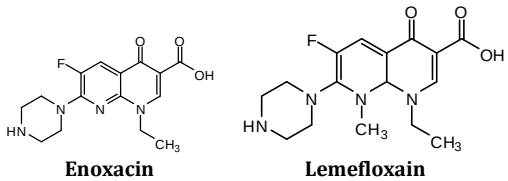


Nalidixic acid **Cinoxacin** **Oxolinic acid**

Figure 1a: Structure of some first generation quinolone derivatives

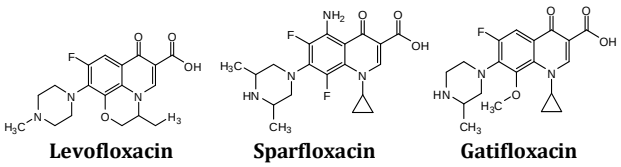


Ciprofloxacin **Ofloxacin** **Norfloxacin**



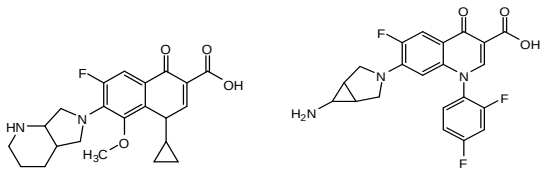
Enoxacin **Lemefloxain**

Figure 1b: Structure of some second generation quinolone derivatives



Levofloxacin **Sparfloxacin** **Gatifloxacin**

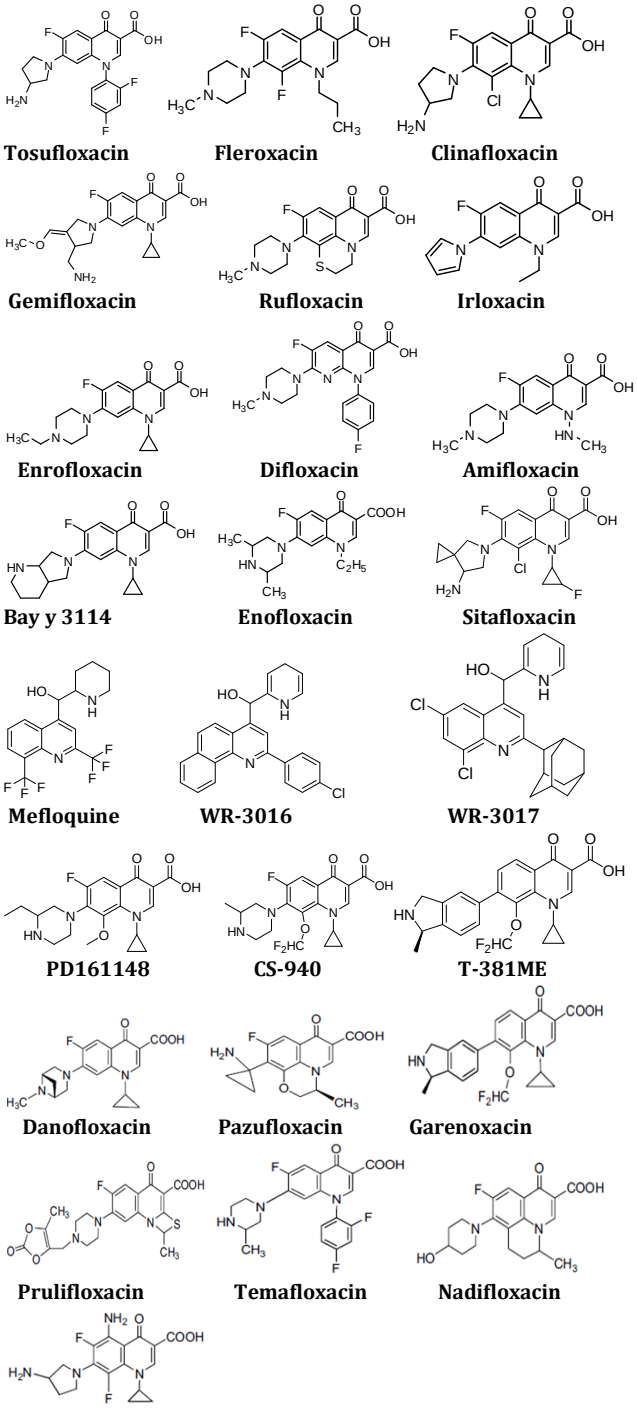
Figure 1c: Structure of some third generation quinolone derivatives



Moxifloxacin **Trovafloxacin**

Figure 1d: Structure of some fourth generation quinolone derivatives

Figure 1: Structure of first (1a), second (1b), third (1c) and fourth (1d) generation quinolone derivatives.



Tosufloxacin **Fleroxacin** **Clinafloxacin**

Gemifloxacin **Rufloxacin** **Irloxacin**

Enrofloxacin **Difloxacin** **Amifloxacin**

Bay y 3114 **Enofloxacin** **Sitafloxacin**

Mefloquine **WR-3016** **WR-3017**

PD161148 **CS-940** **T-381ME**

Danofloxacin **Pazufloxacin** **Garenoxacin**

Prulifloxacin **Temafloxacin** **Nadifloxacin**

PD 124816

Figure 2: Structure of some newer quinolone derivatives

2.1 Pharmacology

The basic pharmacophore, or active structure, of the fluoroquinolone (FQL) class is based upon the quinoline ring system [10]. The addition of the fluorine atom at C6 distinguishes the successive-generation FQLs from the first-generation quinolones. The addition of the C6 fluorine atom has since been demonstrated to not be required for the antibacterial activity of this class [11]. Various substitutions made to the quinoline ring resulted in the development of numerous FQL drugs available today. Each substitution is associated with a number of specific adverse reactions, as well as increased activity against bacterial infections, whereas the quinoline ring, in and of itself, has been associated with severe and even fatal adverse reactions [12].

2.2 Generations

Researchers divide the quinolones into generations based on their antibacterial spectrum [13]. The earlier-generation agents are, in general, more narrow-spectrum than the later ones, but no standard is employed to determine which drug belongs to which generation. The only universal standard applied is the grouping of the non-fluorinated drugs found within this class (quinolones) within the 'first-generation' heading. The first generation is rarely used today. Nalidixic acid was list as a carcinogen on 15 May 1998 [14]. A number of the second-, third-, and fourth-generation drugs have been removed from clinical practice due to severe toxicity issues or discontinued by their manufacturers. The first generation is rarely used today. The drugs most frequently prescribed today consist of moxifloxacin, ciprofloxacin, levofloxacin and, to some extent, their generic equivalents.

First-generation: Various first generation quinolones such as cinoxacin, flumequine (veterinary use), nalidixic acid, oxolinic acid, piromidic acid, pipemidic acid, and rosoxacin [15]

Second-generation: The second-generation class is sometimes subdivided into Class 1 and Class 2 [15,16]. Examples are ciprofloxacin, enoxacin, fleroxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin and rufloxacin,

Third-generation: Unlike the first- and second-generations, the third-generation is active against streptococci [15,16]. Examples are balofloxacin, Grepafloxacin, levofloxacin, pazufloxacin, sparfloxacin, temafloxacin, and tosufloxacin.

Fourth-generation: Fourth-generation fluoroquinolones act at DNA gyrase and topoisomerase IV. This dual action slows development of resistance (15-16). This dual action slows development of resistance. Examples are clinafloxacin, gatifloxacin, gemifloxacin, moxifloxacin, sitafloxacin, trovafloxacin and prulifloxacin.

In development: delafloxacin (an anionic fluoroquinoline in clinical trials), JNJ-Q2 (completed Phase II for MRSA), nemonoxacin.

2.3 Medical uses

Fluoroquinolones (FQLs) are broad-spectrum antibiotics (effective against both gram-negative and gram-positive bacteria) that play an important role in treatment of bacterial infections (especially hospital-acquired and resistance strains to older antibacterial). The use of broad-spectrum antibiotics encourage the spread of multidrug-resistant (MDR) strains and recommend minimizing the use of FQLs and other broad-spectrum antibiotics in less severe infections and in those in which risk factors for MDR are not present. FQLs are featured prominently for the treatment of hospital-acquired pneumonia [17]. The FQLs not be used as a first-line agent for community-acquired pneumonia [18] instead recommending macrolide or doxycycline as first-line agents. The Drug-Resistant *Streptococcus pneumoniae* Working Group recommends FQLs be used for the ambulatory treatment of community-acquired pneumonia only after other antibiotic classes have been tried and failed, or in those with demonstrated drug-resistant *S. neumoniae* [19]. The FQLs are often used for genitourinary infections, and are widely used in the treatment of hospital-acquired infections associated with urinary catheters. In community-acquired infections, they are recommended only when risk factors for MDR are present or after other antibiotic regimens have failed. However, for serious acute cases of pyelonephritis or bacterial prostatitis where the patient may need to be hospitalised,

FQLs are recommended as first-line therapy [20]. Due to sickle-cell disease patients' being at increased risk for developing osteomyelitis from the *Salmonella* genus, FQLs are the "drugs of choice" due to their ability to enter bone tissue without chelating it, as tetracyclines are known to do.

Veterinary use: The quinolones have been widely used in agriculture, and several agents have veterinary, but not human, applications. For veterinary uses: danofloxacin, difloxacin, enrofloxacin, ibafloxacin, marbofloxacin, orbifloxacin, sarafloxacin. However, the agricultural use of FQLs has been restricted since 1997, due to concerns over the development of antibiotic resistance [

2.4 Adverse effects of fluoroquinolones:

In general, fluoroquinolones (FQLs) are well tolerated, with most side-effects being mild to moderate [21]. On occasion, serious adverse effects occur [22]. Common side-effects include gastrointestinal effects such as nausea, vomiting, and diarrhea, as well as headache and insomnia. The overall rates of adverse events are roughly similar to seen in patients treated with other antibiotics [23-25]. Patients treated with FQLs experienced adverse events severe enough than those treated with cephalosporins or macrolides, but less frequently than those treated with penicillins, clindamycin, sulfonamides, or vancomycin [26]. A variety of relatively rare but serious adverse effects those are associated with all members of the FQL antibacterial class. Among these, tendon problems and exacerbation of the symptoms of the neurological disorder myasthenia gravis is the subject of warnings. The most severe form of tendonopathy associated with FQL administration is tendon rupture, which involves the Achilles tendon. Younger people experience good recovery, but permanent disability is possible, and is more likely in older patients [27]. The frequency of FQL-associated Achilles tendon rupture in patients treated with ciprofloxacin or levofloxacin is has been estimated at 17 per 100,000 treatments [21,28]. Risk is substantially elevated in the elderly and in those with recent exposure to corticosteroid therapy. Simultaneous use of corticosteroids is present in almost one-third of quinolone-associated tendon rupture [29]. Tendon damage may manifest during, as well as up to a year after FQL therapy has been completed [30]. FQs prolong the QT interval by blocking voltage-gated potassium channels [31]. Prolongation of the QT interval can lead to torsades de pointes, a life-threatening arrhythmia, but in practice this appears relatively uncommon in part because the most widely prescribed FQLs (ciprofloxacin and levofloxacin) only minimally prolong the QT interval [32]. *Clostridium difficile*-associated diarrhea may occur in connection with the use of any antibacterial drug, especially with broad spectrum drugs like clindamycin, cephalosporins, and FQLs. The FQLs associated risk is simlar to [33] or less [34] than that associated with broad spectrum cephalosporins. The FQL administration may be associated with the acquisition and outgrowth of a particularly virulent *Clostridium* strain [35]. The neurotoxicity occurs in approximately 1% to 4.4% of patients taking FQs, with serious adverse effects occurring less than 0.5%.**(**24**)** The most important of these may be peripheral neuropathy, which can be permanent. Other nervous system effects include insomnia, restlessness, and rarely, seizure, convulsions, and psychosis [36]. Other rare and serious adverse events have been observed with varying degrees of evidence for causation [37-40]**.** Events that may occur in acute overdose are rare, and include renal failure and seizure [41]. Susceptible groups of patients, such as children and the elderly, are at greater risk of adverse reactions during therapeutic use [42].

Fluoroquinolones disadvantages or side effects

- Tendonitis or tendon rupture
- Multiple drug interactions
- Not used in children
- Newer quinolones produce additional toxicities to the heart that were not found with the older agents
- Gastrointestinal effects
- CNS effects: Headache, dizziness, and drowsiness have been reported with all fluoroquinolones.
- Phototoxicity: The degree of phototoxic potential of fluoroquinolones is as follows: lomefloxacin>sparfloxacin>ciprofloxacin>norfloxacin=ofloxacin=levofloxacin=gatiflox-cin = moxifloxacin.
- Musculoskeletal effects.
- Hepatoxicity
- Cardiovascular effects
- Hypoglycemia/Hyperglycemia
- Hypersensitivity

Fluoroquinolone advantages:

- Ease of administration
- Daily or twice daily dosing
- Excellent oral absorption
- Excellent tissue penetration
- Prolonged half-lives
- Significant entry into phagocytic cells
- Efficacy
- Overall safety

2.5 Contraindications

Quinolones are contraindicated if a patient has epilepsy, QT prolongation, pre-existing CNS lesions, or CNS inflammation, or the patient has suffered a stroke [22]. The safety concerns of FQL use during pregnancy and, as a result, are contraindicated except for when no other safe alternative antibiotic exists [43]. However, the outcome of pregnancies involving quinolone use in the first trimester found no increased risk of malformations [44]. They are also contraindicated in children due to the risks of damage to the musculoskeletal system [45]. Their use in children is not absolutely contraindicated, however. For certain severe infections where other antibiotics are not an option, their use can be justified [46]. Quinolones should also not be given to people with a known hypersensitivity to the drug [47]. Quinolone antibiotics should not be administered to patients who are dependent on benzodiazepines, since they compete directly with benzodiazepines at the GABA-A receptor, acting as a competitive antagonist and thus possibly precipitating a severe acute and potentially fatal withdrawal effect [48-51].

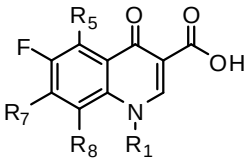
2.6 Mechanism of action

Quinolones and fluoroquinolones (FQLs) are chemotherapeutic bactericidal drugs, eradicating bacteria by interfering with DNA replication. Quinolones inhibit the bacterial DNA gyrase or the topoisomerase II ligase, thereby inhibiting DNA replication and transcription. Recent evidence has shown topoisomerase II is also a target for a variety of quinolone-based drugs. Thus far, most of the compounds that show high activity against the eukaryotic type II enzyme contain aromatic substituents at their C-7 positions [52,53]. Quinolones can enter cells easily and, therefore, are often used to treat intracellular pathogens such as *Legionella pneumophila* and *Mycoplasma pneumoniae*. For many Gram-negative bacteria, DNA gyrase is the target, whereas topoisomerase IV is the target for many Gram-positive bacteria. It is believed eukaryotic cells do not contain DNA gyrase or topoisomerase IV. However, there is debate concerning whether the quinolones still have such an adverse effect on the DNA of healthy cells. The FQLs inhibit the topoisomerase II ligase domain, leaving the two nuclease domains intact. This modification, coupled with the constant action of the topoisomerase II in the bacterial cell, leads to DNA fragmentation via the nucleasic activity of the intact enzyme domains. Some compounds in this class have been shown to inhibit the synthesis of mitochondrial DNA [54-56].

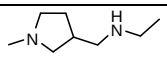
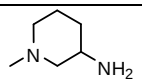
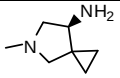
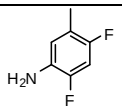
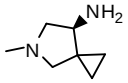
Mechanism of toxicity: The mechanisms of the toxicity of FQLs has been attributed to their interactions with different receptor complexes, such as blockade of the GABAa receptor complex within

the central nervous system, leading to excitotoxic type effects [22] and oxidative stress [57].

Interactions: Theophylline, nonsteroidal anti-inflammatory drugs and corticosteroids enhance the toxicity of FQLs [58.59]. Products containing multivalent cations, such as aluminium- or magnesium-containing antacids and products containing calcium, iron, or zinc, invariably result in marked reduction of oral absorption of FQLs [60]. Taking colloidal silver along with several versions of quinolones might decrease how much antibiotic the body absorbs [61]. Other drugs that interact with FQLs include antacids, sucralfate, probenecid, cimetidine, warfarin, antiviral agents, phenytoin, cyclosporine, rifampin, pyrazinamide, and cycloserine [62]. Many FQLs, especially ciprofloxacin, inhibit the cytochrome P450 isoform CYP1A2. This inhibition causes an increased level of drugs that are metabolized by this enzyme. This includes antidepressants such as amitriptyline and imipramine, clozapine (an atypical antipsychotic), caffeine, olanzapine (antipsychotic), ropivacaine (local anaesthetic), theophylline, and zolmitriptan (serotonin receptor agonist).



Some recent trends in chemical modification

Compounds	R_1	R_5	R_7	R_8
Merafloxacin	$-C_2H_5$	H		F
Balofloxacin		H		OCH_3
Olafloxacin		H		CH_3
Wq-2944		NH_2	-NH-CH_3	CH_3
DK-507K		H		OCH_3

Structure-Activity Relationship:

Position 1:

- Earlier study indicated that substitution at N-1 position is important for Anti-bacterial activity.
- QSAR analysis of a set of N-1 allyl and alkyl derivatives suggested and optimum STERIMOL length of 0.42 nm, corresponding approximately to an ethyl group.
- STERIMOL is a program that calculates a set of five parameters characterizing size and shape of a substituent.
- STERIMOL length is defined as length of substituent along the axis of bond between the substituent and the parent molecule.
- Subsequently, the discovery of potent quinolones with N-1 phenyl and N-1 cyclopropyl substitutions indicated that with respect to an N-1 substituent, in addition to steric bulk , there are other factors such as electronic- π donation and ideal spatial effects that also have a great influence on their biological activities .
- Introduction of a t-butyl group at N-1 produced quinolones with enhanced activity against gram positive bacteria with minor reduction of activity against gram negative bacteria.
- In general , cyclopropyl group appears to be optimum for activity. e.g Ciprofloxacin.

Position-3:

- Position 3 and 4, having a link between the carboxylic acid group and the keto group are generally considered necessary for binding of quinolones to DNA gyrase.
- Classical studies have produced no active quinolone with a significant modification of C-3 carboxylic acid group, with exception of groups which are converted in vivo to carboxylic acid group.

Position-4:

- Position-4 has not been extensively explored and replacement of 4- keto group with other groups has generally produced inactive or weakly active compounds.

Position-5:

- Compounds with small substituents such as nitro, amino, halo, alkyl groups have been synthesized. Among them, C-5 amino group enhances absorption and / or tissue distribution . e.g Sparfloxacin.
- The incidence of photo toxicity of Sparfloxacin is the lowest of the fluoroquinolones , because of the presence of the 5-amino group , which counteracts the effect of the 8- fluoro substituent .

Position-6:

- Of various C-6 substituents, H, Cl, Br, F, CH_3, S- CH_3, CO CH_3, CN, NO_2 etc the addition of a fluorine atom resulted in a dramatic increase in anti-bacterial potency.
- Fluoro group at C-6 seems to improve both the DNA gyrase complex binding (2 to 17 folds) and cell penetration (1 to 70 folds) of the corresponding derivatives with no substitution at C-6.

Position-7:

- C-7 piperazinyl group in addition to C-6 fluorine substituent has anti-bacterial potency for superior to that of earlier classical quinolones against both gram-positive and gram-negative bacteria.
- In general, quinolones with small or linear C-7 substituents (H, Cl, CH_3, NH_2-CH_2-CH_2- NH_2, NH- CH_3, NH-NH_2)
- Possess moderate to weak anti-bacterial activities.
- Various substitutions tried at C-7 position are-
- substituted piperazinyl
- substituted pyrrolidinyl
- substituted morpholinyl
- In general, the substitution of methyl at C-4 position of the piperazinyl group enhances gram-positive anti-bacterial activity with slight decrease in gram-negative activity.

Position -8:

- C-8 fluoro or chloro derivatives are more active in-vivo, owing to better oral absorption.
- Oxygen substituent at C-8 position, where substituent is part of ring system has been shown to have better in vivo efficacy .
- C-8 methoxy or ethoxy group appears to increase the spectrum of activity.
- C-8 methoxy (e.g Gatifloxacin) has been shown to contribute significant activity against anaerobes.

Antibiotic misuse and bacterial resistances: Resistance to quinolones can evolve rapidly, even during a course of treatment. Numerous pathogens, including *Staphylococcus aureus*, enterococci, and *Streptococcus pyogenes* now exhibit resistance worldwide. Widespread veterinary usage of quinolones, in particular in Europe, has been implicated [63]. Fluoroquinolones (FQLs) have been recommended to be reserved for the use in patients that are seriously ill and may soon require immediate hospitalization [64]. Though considered to be very important and necessary drugs required to treat severe and life-threatening bacterial infections, the associated antibiotic misuse remains unchecked, which has contributed to the problem of bacterial resistance. The overuse of antibiotics such as happens with children suffering from otitis media (ear infections) has given rise to a breed of super-bacteria that are resistant to antibiotics entirely [65]. For example, the use of the FQLs had increased threefold in an emergency room environment in the United States between 1995 and 2002, while the use of safer alternatives, such as macrolides, declined significantly [19]. FQLs had become the most commonly prescribed class of antibiotics to adults in 2002. Nearly half (42%) of these prescriptions were for conditions, such as acute bronchitis, otitis media, and acute upper respiratory tract infection

[66]. In addition, they are commonly prescribed for medical conditions, such as acute respiratory illness, that are usually caused by viral infections [67,68]. Three mechanisms of resistance are known [69]. Some types of efflux pumps can act to decrease intracellular quinolone concentration [70]. In Gram-negative bacteria, plasmid-mediated resistance genes produce proteins that can bind to DNA gyrase, protecting it from the action of quinolones. Finally, mutations at key sites in DNA gyrase or topoisomerase IV can decrease their binding affinity to quinolones, decreasing the drugs' effectiveness. All FQLs antibacterial drugs describe the serious side effect of peripheral neuropathy. This serious nerve damage potentially caused by FQLs may occur soon after these drugs are taken and may be permanent. Only those taken by mouth or injection were covered by the alert, while those used topically on the eyes and ears were not. Several advocacy groups have petitioned the FDA to increase the prominence of adverse effect warnings on the labels of FQL antibacterials, and to withdraw others from the market [71-74]. Fluoroquinolone (FQL) antibiotics increased risk of developing tendonitis and tendon rupture in patients of all ages taking FQLs for systemic use. This risk is increased in the individuals who are over 60 years of age, taking corticosteroid drugs, and have kidney, heart, or lung transplants. FQLs, due to their neuromuscular blocking activity, may exacerbate muscle weakness in persons with myasthenia gravis. Serious adverse events, including deaths and requirement for ventilatory support, have been reported in this group of patients. Avoidance of FQLs in patients with known history of myasthenia gravis is advised [75-77].

References

[1] Andriole, VT The Quinolones. Academic Press, 1989.

[2] Andersson, MI, MacGowan, AP. Development of the quinolones. *J. Antimicrob. Chemother*. 2003; 51(Suppl. S1): 1-11.

[3] Ivanov DV, Budanov SV. Ciprofloxacin and antibacterial therapy of respiratory tract infections. *Antibiot. Khimioter.* 2006; 51(5): 29–37.

[4] Sanofi-aventis U.S. LLC (September 2008). NegGram Caplets (nalidixic acid, USP). USA: FDA. Retrieved 6 May 2011.

[5] Wentland MP: In memoriam: George Y. Lesher, in Hooper DC, Wolfson JS (eds): Quinolone antimicrobial agents, ed 2, Washington DC, American Society for Microbiology: XIII - XIV, 1993.

[6] Hooper DC. Emerging mechanisms of fluoroquinolone resistance. *Emerg Infect Dis,* 2001; 7(2): 337–41.

[7] Norris, S; Mandell, GL. The quinolones: history and overview. *The quinolones: history and overview*. San Diego: Academic Press Inc. 1988; pp. 1–22.

[8] Stacy J, Childs, MD. Safety of the Fluoroquinolone Antibiotics: Focus on Molecular Structure. *Infect Urol*, 2000, 13 (1): 3–10.

[9] New Classification and Update on the Quinolone Antibiotics- May 1, 2000, American Academy of Family Physicians. Retrieved 18 March 2008.

[10] Schaumann R, Rodloff A. C. Activities of Quinolones Against Obligately Anaerobic Bacteria. *Anti-Infective Agents in Medicinal Chemistry,* 2007; 6 (1): 49–56.

[11] Chang YH, Se HK, Young KK. Novel 5-amino-6-methylquinolone antibacterials: A new class of non-6-fluoroquinolones. *Bioorg & Med Chem Lett*, 1997; 7(14): 1875–1878.

[12] Cann HM, Verhulst HL. Fatal acute chloroquine poisoning in children. *Pediatrics,* 1961; 27 (1): 95–102.

[13] Ball P. Quinolone generations: natural history or natural selection?. *J. Antimicrob. Chemother*. 2000; 46 (Supplement 3): 17–24.

[14] Holden HE, Barett JF, Huntington CM, Muehlbauer PA, Wahrenburg MG. Genetic profile of a nalidixic acid analog: a model for the mechanism of sister chromatid exchange induction. *Environ Mol Mutagen,* 1989; 13 (3): 238–52.

[15] Oliphant CM, Green GM. Quinolones: a comprehensive review. *Am Fam Physician,* 2002; 65 (3): 455–64.

[16] Ambrose PG, Owens RCJr. Clinical Usefulness of Quinolones. *Seminars in Respiratory and Critical Care Medicine* (Medscape), 1 March 2000.

[17] Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med,* 2005; 171 (4): 388–416.

[18] Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin. Infect. Dis*. 2007; 44 Suppl 2: S27–72.

[19] MacDougall C, Guglielmo BJ, Maselli J, Gonzales R. Antimicrobial drug prescribing for pneumonia in ambulatory care. *Emerging Infect. Dis.* 2005; 11 (3): 380–4.

[20] Liu H, Mulholland SG. Appropriate antibiotic treatment of genitourinary infections in hospitalized patients. *Am J Med*. 205; 118 Suppl 7A(7): 14S–20S.

[21] Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis,* 2005; 41(Suppl 2): S144–57.

[22] De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones. an overview on mechanistic aspects. *Curr. Med. Chem.* 2001; 8 (4): 371–84.

[23] Skalsky K, Yahav D, Lador A, Eliakim-Raz N, Leibovici L, Paul M. Macrolides vs. quinolones for community-acquired pneumonia: meta-analysis of randomized controlled trials. *Clin Microbiol Infect,* 2013; 19 (4): 370–8.

[24] Falagas ME, Matthaiou DK, Vardakas KZ. Fluoroquinolones vs beta-lactams for empirical treatment of immunocompetent patients with skin and soft tissue infections: a meta-analysis of randomized controlled trials. *Mayo Clin Proc,* 2006; 81 (12): 1553–66.

[25] Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Saf* , 2009; 32(5): 359-78.

[26] Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin. Infect. Dis.* 2008; 47(6): 735–43.

[27] Kim GK. The Risk of Fluoroquinolone-induced Tendinopathy and Tendon Rupture: What Does The Clinician Need To Know?. *J Clin Aesthet Dermatol* 2010; 3(4): 49–54.

[28] Sode J, Obel N, Hallas J, Lassen A. Use of fluroquinolone and risk of Achilles tendon rupture: a population-based cohort study. *Eur J Clin. Pharmacol.* 2007; 63 (5): 499–503.

[29] Khaliq Y, Zhanel GG. Musculoskeletal injury associated with fluoroquinolone antibiotics. *Clin Plast Surg,* 2005; 32 (4): 495–502.

[30] Saint F, Salomon L, Cicco A, de la Taille A, Chopin D, Abbou CC. Tendinopathy associated with fluoroquinolones: individuals at risk, incriminated physiopathologic mechanisms, therapeutic management. *Prog. Urol.* 2001; 11 (6): 1331–4.

[31] Heidelbaugh JJ, Holmstrom H. The perils of prescribing fluoroquinolones. *J Fam Pract,* 2013; 62(4): 191–7.

[32] Rubinstein E, Camm J. Cardiotoxicity of fluoroquinolones. *J Antimicrob Chemother,* 2002; 49 (4): 593–6.

[33] Deshpande A, Pasupuleti V, Thota P, *et al.,* Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. *J. Antimicrob. Chemother.* 2013; 68(9): 1951-61.

[34] Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *J Antimicrob Chemother*. 2013; doi:10.1093/jac/dkt477.

[35] Vardakas KZ, Konstantelias AA, Loizidis G, Rafailidis PI, Falagas ME. Risk factors for development of *Clostridium difficile* infection due to BI/NAP1/027 strain: a meta-analysis. *Int J Infect Dis,* 2012; 16 (11): e768–73.

[36] Galatti L, Giustini SE, Sessa A, *et al.*, Neuropsychiatric reactions to drugs: an analysis of spontaneous reports from general practitioners in Italy. *Pharmacol. Res.* 2005; 51(3): 211–6.

[37] Babar S. SIADH Associated With Ciprofloxacin. *The Annals of Pharmacotherapy*, 2013; 47 (10): 1359-1363.

[38] Rouveix B. Clinically significant toxicity and tolerance of the main antibiotics used in lower respiratory tract infections. *Med Mal Infect,* 2006; 36 (11–12): 697–705.

[39] Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Annals of Pharmacotherapy* 2007; 41(11): 1859–66.

[40] Jones SF, Smith RH. Quinolones may induce hepatitis. *BMJ,* 1997; 314 (7084): 869.

[41] Lewis HN, Neal F, Lewis RG, Louis HR; Deems HM, Lewin NA. *Goldfrank's toxicologic emergencies*. New York: McGraw-Hill, Medical Pub. Division, 2006. ISBN 0-07-143763-0.

[42] Iannini PB. The safety profile of moxifloxacin and other fluoroquinolones in special patient populations. *Curr Med Res Opin,* 2007; 23 (6): 1403–13.

[43] Nardiello S, Pizzella T, Ariviello R. Risks of antibacterial agents in pregnancy. *Infez Med,* 2002; 10 (1): 8–15.

[44] Bar-Oz B, Moretti ME, Boskovic R, O'Brien L, Koren G. The safety of quinolones-a meta-analysis of pregnancy outcomes. *Eur J Obstet Gynecol Reprod Biol,* 2009; 143(2):75-8.

[45] Noel GJ, Bradley JS, Kauffman RE, Duffy CM, Gerbino PG, Arguedas A, Bagchi P, Balis DA, Blumer JL. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. *Pediatr Infect Dis J,* 2007; 26 (10): 879–91.

[46] Leibovitz, E.; Dror, Yigal. The use of fluoroquinolones in children. *Current Opinion in Pediatrics,* 2006; 18 (1): 64–70.

[47] Scherer K, Bircher AJ. Hypersensitivity reactions to fluoroquinolones. *Curr Allergy Asthma Rep,* 2005; 5 (1): 15–21.

[48] Unseld E, Ziegler G, Gemeinhardt A *et al.* Possible interaction of fluoroquinolones with the benzodiazepine-GABAA-receptor complex. *Br J Clin Pharmacol,* 1990; 30: 63–70.

[49] John Girvan McConnell. Benzodiazepine tolerance, dependency, and withdrawal syndromes and interactions with fluoroquinolone antimicrobials. Br J Gen Pract. 2008 May 1; 58(550): 365–366.

[50] Halliwell RF, Davey PG, Lambert JJ. Antagonism of GABAA receptors by 4-quinolones. *J Antimicrob Chemother.* 1993; 31:457–462.

[51] Risk of fluoroquinolone-associated Myasthenia Gravis Exacerbation February 2011 Label Changes for fluoroquinolones FDA, online access 16 March 2011

[52] Elsea SH, Osheroff N, Nitiss JL. Cytotoxicity of quinolones toward eukaryotic cells. Identification of topoisomerase II as the primary cellular target for the quinolone CP-115,953 in yeast. *J Biol Chem,* 1992; 267(19): 13150–3.

[53] Pommier Y, Leo E, Zhang H, Marchand C. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. *Chem. Biol,* 2010; 17: 421-433.

[54] Kaplowitz, Neil. Hepatology highlights. *Hepatology,* 2005; 41(2): 227.

[55] Enzmann H, Wiemann C, Ahr HJ, Schlüter G. Damage to mitochondrial DNA induced by the quinolone Bay y 3118 in embryonic turkey liver. *Mutat Res* 1999; 425 (2): 213–24.

[56] Suto MJ, Domagala JM, Roland GE, Mailloux GB, Cohen MA. Fluoroquinolones: relationships between structural variations, mammalian cell cytotoxicity, and antimicrobial activity. *J Med Chem,* 1992; 35 (25): 4745–50.

[57] Saint F, Gueguen G, Biserte J, Fontaine C, Mazeman E. Rupture of the patellar ligament one month after treatment with fluoroquinolone. *Rev Chir Orthop Reparatrice Appar Mot*, 2000; 86 (5): 495–7.

[58] Moderate Interaction: Quinolones/Corticosteroids. Medscape. Retrieved 2 September 2008.

[59] Cohen JS. Peripheral Neuropathy Associated with Fluoroquinolones. *Annals of Pharmacotherapy,* 2001; 35 (12): 1540–7.

[60] Fluoroquinolone Adverse Effects and Drug Interactions: Drug-Drug Interactions Author from: the Department of Pharmacy Practice, School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado. Retrieved on 17 December 2009.

[61] Johns CM; Tracy TS. Colloidal Silver. *Forensic Science and Medicine*: 2003; 87–90.

[62] Fluoroquinolone Adverse Effects and Drug Interactions. Medscape. Retrieved 2 September 2008.

[63] Nelson JM, Chiller TM, Powers JH, Angulo FJ. Fluoroquinolone-resistant Campylobacter species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. *Clin Infect Dis,* 2007; 44 (7): 977–80.

[64] Jim Hoover, for Bayer Corporation, Alaska Pharmacy and Therapeutics Committee 19 March 2004

[65] Froom J, Culpepper L, Jacobs M, *et al.* Antimicrobials for acute otitis media? A review from the International Primary Care Network. *BMJ* 1997; 315 (7100): 98–102.

[66] Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribing in the United States: 1995 to 2002. *The American Journal of Medicine,* 2005; 118 (3): 259–68..

[67] Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA: the Journal of the American Medical Association,* 2003; 289 (7): 885–8.

[68] Lautenbach E, Larosa LA, Kasbekar N, Peng HP, Maniglia RJ, Fishman NO. Fluoroquinolone utilization in the emergency departments of academic medical centers: prevalence of, and risk factors for, inappropriate use. *Arch. Intern. Med.* 2003; 163 (5): 601–5.

[69] Robicsek A, Jacoby GA, Hooper DC (October 2006). The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect Dis* 6 (10): 629–40.

[70] Morita Y, Kodama K, Shiota S, Mine T, Kataoka A, Mizushima T, Tsuchiya T (July 1998). NorM, a Putative Multidrug Efflux Protein, of Vibrio parahaemolyticus and Its Homolog in Escherichia coli. *Antimicrob. Agents Chemother.* 42 (7): 1778–82.

[71] Sasich LD, Wolfe SM, Zieve A, Christen P, Christen B. (9 June 1998). Petition to the Food and Drug Administration to immediately stop the distribution of dangerous, misleading prescription drug information to the public. (HRG Publication #1442). USA: Public Citizen.

[72] Jacobs M, Worldwide Overview of Antimicrobial Resistance. International Symposium on Antimicrobial Agents and Resistance 2005.

[73] Bergan T, Bayer. Pharmacokinetics of fluorinated quinolones. *Academic Press*: 1988; 119–154.

[74] Bergan T, Dalhoff A, Thorsteinsson SB. *A review of the pharmacokinetics and tissue penetration of ciprofloxacin*. 1985; 23-36.

[75] Castora FJ, Vissering FF, Simpson MV. The effect of bacterial DNA gyrase inhibitors on DNA synthesis in mammalian mitochondria. *Biochim Biophys Acta,* 1983; 740(4): 417-27.

[76] Evelyn RF. Public health service food and drug administration center for drug evaluation and research (1 March 2005). Consult: One-Year Post Pediatric Exclusivity Postmarketing Adverse Events Review. USA: FDA. Retrieved 31 August 2009.

[77] Baker J; Wolfe S, Lurie P. (1 May 2006). Petition to the FDA to Immediately Ban the Antibiotic Gatifloxacin (Tequin) (HRG Publication #1768). USA: Public Citizen.

